FROM THE ANALYST'S COUCH

Advances in prostate cancer treatment

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Prostate cancer is the second most common cancer in men worldwide[1]. Outcomes for patients with early-stage prostate cancer (stage I/II) are good, with over 90% progression-free survival after 5 years. However, for patients diagnosed at stage III and stage IV, the likelihood of a cure is low.

Current treatments

For stage I–III patients the standard treatment includes surveillance, prostatectomy and radiotherapy. For all stage IV and high-risk stage III patients, androgen ablation by surgical or chemical castration can bring about sustained remission. First-generation anti-androgens such as flutamide and bicalutamide assist in this setting. However, castration resistance, which is characterized by genomic mutations in the androgen receptor (AR)[2], inevitably develops in the stage IV setting, at which point the prognosis is poor. The historic standard treatment for metastatic castration-resistant prostate cancer (CRPC), docetaxel, provides a median overall survival improvement of roughly 3 months.

Several new products came to market in recent years. Two anti-androgen products, abiraterone (Zytiga; Janssen) and enzalutamide (Xtandi; Medivation/Astellas), approved in 2011 and 2012, respectively, represented major advances. Abiraterone lowers levels of serum testosterone by inhibiting cytochrome P17, a crucial enzyme in the production of testosterone. Enzalutamide targets the AR directly and competitively inhibits androgen binding. It has a higher affinity for the AR than the first-generation non-steroidal anti-androgens. However, the emergence of mutations (such as a single F876L amino acid substitution) in the AR can confer resistance. Market access is also limited by their expensive pricing patterns (enzalutamide costs US$89,000 a year in the United States).

Cancer vaccines represent a very different approach. They are defined by their ability to stimulate a generalized immune response against the tumour rather than being directly cytotoxic. In 2011, sipuleucel-T (Provenge; Dendreon), an autologous dendritic cell-based immunotherapy, was approved for first-line usage in patients with asymptomatic or minimally symptomatic metastatic CRPC, making it the first therapeutic cancer vaccine to be approved in the United States. However, it has underperformed in terms of early sales, with likely barriers being lingering doubts about the quality of its key clinical trial, its $93,000 annual cost and its complex administration process, balanced against a modest efficacy benefit.

Approved in 2013, the radioactive calcium mimetic radium-223 dichloride (Xofigo; Bayer), which specifically targets bone metastases (present in 80–90% of patients with metastatic CRPC), is the newest treatment for CRPC.

Other recent approvals are the receptor activator of NF-κB (RANK) ligand inhibitor denosumab (Xgeva; Amgen), which targets bone metastases by increasing bone growth, and the taxane cabazitaxel (Jevtana; Sanofi); both have had a limited impact on this indication owing to modest efficacy profiles.

There is an unmet need for products that provide a greater survival benefit than current treatment regimens.

The developmental pipeline

The pipeline for prostate cancer is large and diverse (TABLE 1). Most agents are developed for the treatment of CRPC. Although some products, such as ARN-509 (Aragon Pharmaceuticals; Phase II), use established mechanisms of action such as direct AR inhibiton, the majority of late-stage pipeline molecules act on a highly diverse range of novel molecular targets (FIG. 1). In addition to small molecules, autologous cell vaccination, viral-based vaccines and monoclonal antibodies are being developed.

The class of dendritic-cell-based vaccines is diversifying, with viral-based vectors — which do not require the time-consuming dendritic cell extraction procedures associated with Provenge — in Phase III development. These include rilimogene galvacirepvec (Prostvac; Bavarian Nordic) for hormone-sensitive metastatic prostate cancer and AdV-tk + valacyclovir (Prostatak; Advantagene) in the localized setting. Rilimogene galvacirepvec showed an unprecedented 8-month overall survival improvement versus placebo in Phase II trials in CRPC — roughly double the 4.1–4.5-month benefit provided by sipuleucel-T.

Owing to their high level of specificity for targets such as growth factor receptors and tumour antigens, there are a number of monoclonal antibodies in the pipeline for CRPC. These include ipilimumab (Yervoy; Bristol-Myers Squibb), which stimulates an immunological response against the tumour by blocking the inhibitory signal of cytotoxic T lymphocyte antigen 4. It was approved in 2011 for the treatment of late-stage melanoma. Although it underperformed in a recent Phase III trial for CRPC, a second Phase III trial is underway in the docetaxel-naive setting, where analyses have shown a potentially greater efficacy benefit.

Late-stage trials of multitargeted small-molecule kinase inhibitors for CRPC, such as cabozantinib (Cometriq; Exelixis), are underway. However, recent Phase III trials that investigated the addition of the multitargeted kinase inhibitors dasatinib (Sprycel; Bristol-Myers Squibb) and ziv-aflibercept (Zaltrap; Regeneron/Sanofi) to docetaxel did not show any improvement in survival.

Finally, the clusterin inhibitor custirsen sodium (OGX-11; Teva Pharmaceutical), which sensitizes tumours to apoptosis in response to chemotherapy, and the calcium channel blocker tasquinimod (ABR-215050; Active Biotech), which alters the tumour microenvironment by modulating regulatory myeloid cell function, are both in Phase III development and exhibit mechanisms of action that are unique in the prostate cancer pipeline. Custirsen sodium is a particularly promising product, extending overall survival by 7 months in CRPC in a Phase II trial. Tasquinimod also showed promising Phase II results in CRPC, slowing disease progression.

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Market outlook

Recent market entries such as abiraterone and enzalutamide improved survival benefits in metastatic CRPC, and further improvements are expected should Phase III products be approved. Cabazitaxel and sipuleucel-T remain viable options for certain patients, although their respective market shares are expected to remain small relative to abiraterone, enzalutamide and docetaxel. In addition, the recent approval of radium-223 dichloride and the potential market entry of AdV-tk + valacyclovir, which targets patient populations that were previously poorly served, will continue to contribute to the changing clinical landscape. The level of competition in this market is expected to increase, although novel products for hormone-sensitive prostate cancer are unlikely to directly compete with products that are approved for CRPC, and vice versa. Overall, the prostate cancer market is expected to grow from $4.1 billion in 2012 to $8.2 billion in 2019. Most of this growth is expected to be in the symptomatic CRPC segment, driven by late-stage pipeline molecules and increasing uptake of recently approved therapies. However, the approvals of drugs such as viral-vector based vaccines in earlier disease settings are also expected to make a growing contribution, particularly towards the end of the decade. Cancer vaccines are expected to become a more prominent drug class.

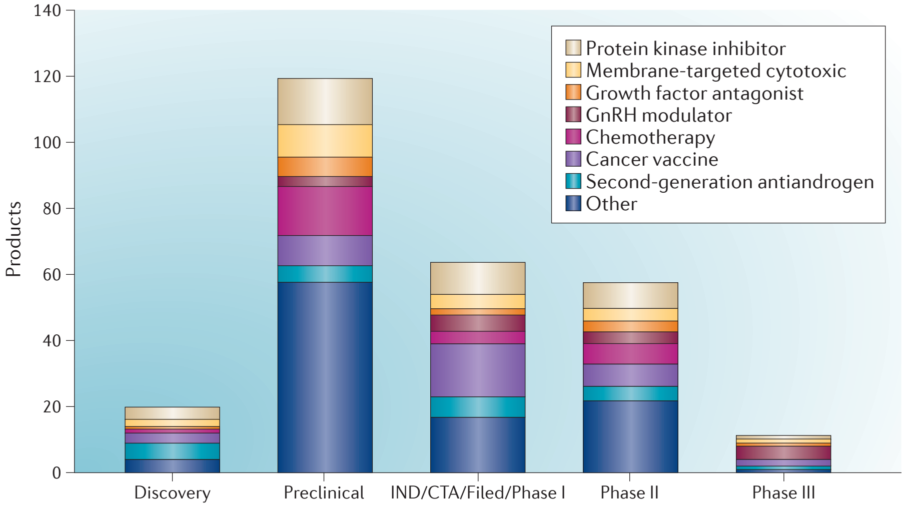

Figure 1 | **Pipeline products by stage of development and mechanism of action.** 'Other' refers to histone deacetylase complex inhibitors, apoptosis activators and cell membrane disruptors, as well as compounds with mechanisms of action that appear three times or fewer in the pipeline. Source: GBI Research Proprietary Database (pipeline molecules). CTA, clinical trial approval; GnRH, gonadotropin-releasing hormone; IND, investigational new drug.

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Competing interests
The authors declare no competing financial interests.

1. Siegel, R. *et al.* Cancer Statistics, 2012. *CA Cancer J. Clin.* **62**, 10–29 (2012).
2. Amaral, T. M. S. *et al.* Castration-resistant prostate cancer: mechanisms, targets, and treatment. *Prostate Cancer* http://dx.doi.org/10.1155/2012/327253 (2012).
3. Cookson, M. S. *et al.* Castration-resistant prostate cancer: AUA Guideline. *American Urological Association* [online], https://www.auanet.org/common/pdf/education/clinical-guidance/Castration-Resistant-Prostate-Cancer.pdf (2013).

Table 1 | **Selected late-stage pipeline products**

Non-proprietary name	Product name or code	Company	Molecule type	Molecular target	Stage of development
Custirsen sodium	OGX-011	Teva Pharmaceutical	Gene therapy	Apolipoprotein J (clusterin)	Phase III
Cabozantinib (S)-malate	Cometriq	Exelixis	Small molecule	Tyrosine kinases	Phase III
Orteronel	TAK-700	Millennium Pharmaceuticals	Small molecule	Cytochrome P17	Phase III
Ipilimumab	Yervoy	Bristol-Myers Squibb	Monoclonal antibody	Cytotoxic T lymphocyte antigen 4 (CTLA4)	Phase III
Tasquinimod	ABR-215050	Active Biotech	Small molecule	S100 calcium binding protein A9 (S100-A9)	Phase III
Rilimogene galvacirepvec	Prostvac	Bavarian Nordic	Vaccine	Kallikrein 3 (KLK3; also known as prostate-specific antigen)	Phase III
AdV-tk + valacyclovir	ProstAtak	Advantagene	Vaccine	DNA vector-based T cell activator	Phase III
Padeliporfin	Tookad Soluble	Steba Laboratories	Small molecule	Nonspecific (light-activated free radical emitter)	Phase III
-	ARN-509	Aragon Pharmaceuticals	Small molecule	Androgen receptor inhibitor	Phase III

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